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Cognitive control network connectivity in adolescent women with and without a parental history of depression



Peter C. Clasen^{a,b,c,*}, Christopher G. Beevers^{a,b,c}, Jeanette A. Mumford^{a,c},
David M. Schnyer^{a,b,c}

^a Department of Psychology, The University of Texas at Austin, United States

^b Institute for Mental Health Research, The University of Texas at Austin, United States

^c Imaging Research Center, The University of Texas at Austin, United States

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ABSTRACT

Background: Adolescent women with a parental history of depression are at high risk for the onset of major depressive disorder (MDD). Cognitive theories suggest this vulnerability involves deficits in cognitive control over emotional information. Among adolescent women with and without a parental history of depression, we examined differences in connectivity using resting state functional connectivity analysis within a network associated with cognitive control over emotional information.

Methods: Twenty-four depression-naïve adolescent women underwent resting state functional magnetic resonance imaging (fMRI). They were assigned to high-risk ($n = 11$) and low-risk ($n = 13$) groups based their parents' depression history. Seed based functional connectivity analysis was used to examine group differences in connectivity within a network associated with cognitive control.

Results: High-risk adolescents had lower levels of connectivity between a right inferior prefrontal region and other critical nodes of the attention control network, including right middle frontal gyrus and right supramarginal gyrus. Further, greater severity of the parents' worst episode of depression was associated with altered cognitive control network connectivity in their adolescent daughters.

Conclusions: Depressed parents may transmit depression vulnerability to their adolescent daughters via alterations in functional connectivity within neural circuits that underlie cognitive control of emotional information.

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1. Introduction

Adolescent women with a parental history of depression are at unusually high risk for major depressive disorder

(MDD). Between the ages of 13 and 15, girls begin to experience depression at twice the rate as boys of the same age (Nolen-Hoeksema and Girgus, 1994; Hankin and Abramson, 2001; Hyde et al., 2008). These rates increase by 2–3-fold among girls who have a parental history of depression (Beardselee et al., 1998; Weissman et al., 2006). Adolescent depression is particularly pernicious, as it frequently leads to chronic and recurrent MDD in adulthood (Lewinsohn et al., 1999; Rao et al., 1999). Thus, there is a clear need to elucidate the mechanisms underlying depression vulnerability in this high-risk, adolescent population.

Neural models of depression broadly implicate deficits in the recruitment of regions associated with cognitive

* Corresponding author at: Department of Psychology, University of Texas at Austin, 108 E. Dean Keeton Avenue A8000, Austin, TX 78712-0187, United States. Tel.: +1 512 475 6817; fax: +1 512 471 5935.

E-mail address: clasen@utexas.edu (P.C. Clasen).

control, particularly control over mood congruent information (e.g., sad images) (Mayberg, 1997; Phillips et al., 2003). These regions include ventral and dorsal lateral prefrontal cortex, anterior cingulate cortex, and posterior parietal cortex (Disner et al., 2011). Recent work using resting state fMRI suggests that current depression is associated with abnormalities in the functional connectivity between these regions, which comprise key nodes of the so-called cognitive control network (CCN) (Schlösser et al., 2008; Vasic et al., 2009; Sheline et al., 2010; Veer et al., 2010; Alexopoulos et al., 2012). Thus, a growing body of evidence supports the idea that CCN function is altered in depression. What remains unclear is whether differences in CCN network are due to current symptomatology or are evident prior to symptom onset. Alterations within the CCN network must predate onset of depression for CCN connectivity to be considered a viable risk factor for depression.

To investigate this possibility, we used seed-based, resting state functional connectivity analysis to explore differences in CCN connectivity among adolescent women with and without a parental history of depression. Our exploration focused specifically on a set of CCN regions implicated in attentional control. Cognitive models of depression posit that deficits in attentional control over emotional stimuli play a key role in depression vulnerability (Beck, 1967; Ingram, 1984; Teasdale, 1988). Behavioral studies suggest that these deficits predict the onset of depression in adults (Beevers and Carver, 2003; Beevers et al., 2011). Recent behavioral work also suggests that a parental history of depression predisposes adolescent women to deficits in attentional control for emotional stimuli (Joormann et al., 2007).

Importantly, difficulty with attentional control over emotional stimuli in depression appears to be associated with functional alterations within the CCN network. An imaging study examining attentional control over emotional information found that depression was associated with altered activity several key CCN regions, including right inferior frontal gyrus (rIFG), right middle frontal gyrus (rMFG), and right supramarginal gyrus (rSMG) (Beevers et al., 2010). The rIFG in particular is thought to play a key role in mediating the success of cognitive control over emotional stimuli (Ochsner and Gross, 2005; Wager et al., 2008). This region has been implicated in behavioral inhibition, suppression of unwanted thoughts, attention shifting, and efforts to reappraise emotional stimuli (Aron et al., 2004; Anderson et al., 2004; Hampshire and Owen, 2006; Hampshire et al., 2010).

Given its important role in the cognitive control over emotion stimuli, we selected the rIFG region as a seed region for functional connectivity analyses in adolescent women with and without a parental history of depression. In addition to this whole brain approach, we performed a region of interest (ROI) analysis using the rMFG and rSMG locations identified in our previous study (Beevers et al., 2010). This analysis allowed us to explore the specificity of deficits in this previously defined network using an unbiased approach. We also supplemented group comparisons with analyses using severity of parents' worst episode of depression as a more continuous index of adolescent

depression risk. This variable was then used to examine connectivity between the rIFG seed and rMFG/rSMG targets in the ROI analysis.

We are not aware of any studies examining functional connectivity within the CCN among adolescents at high risk for depression. Two recent studies suggest that adolescent depression is associated with decreased connectivity within putative resting state networks, including fronto-limbic and default mode networks (Bluhm et al., 2009; Cullen et al., 2009). Results in depressed adults are mixed; there is recent evidence of decreased (Veer et al., 2010; Alexopoulos et al., 2012) and increased connectivity within the CCN (Sheline et al., 2010). This is in contrast to a more consistent pattern of increased DCN connectivity in depressed adults (e.g., Sheline et al., 2010; Greicius et al., 2007).

Based on the adolescent and recent adult depression literature, we predicted that adolescent women at high-risk for MDD by virtue of parental history of depression would demonstrate decreased connectivity within the CCN. More specifically, we expected decreased connectivity between rMFG/rSMG targets and the rIFG seed. We also speculated that severity of parents' worst depressive episode would be associated with lower levels of connectivity between rMFG/rSMG targets and the rIFG seed.

2. Methods

2.1. Sample

The sample included 27 adolescents and one of their adult parents (for 96% of the girls, this was their mother). One individual was removed from analysis due to excessive movement during imaging. Two other individuals were removed from the analysis because we could not confidently assign them to a group (parental history or no parental history) due to conflicting reports about depression history. In both cases, the parent who completed the study materials did not report a history of depression; however, their daughters reported a history of depression in the other parent (who did not participate in the study) on a family history self-report questionnaire. In two cases we could not verify the daughter's self-report using standardized measures (i.e., attempts to have the other parent complete the depression history screening and questionnaire were unsuccessful); therefore, we removed these two individuals from the analysis. As a result, the final sample included 24 adolescent girls between the ages of 13 and 15. Girls were then assigned to high-risk ($n = 11$) and low-risk ($n = 13$) groups based on criteria used to classify their parents' history of depression (see below). There were no significant differences with respect to age and race across vulnerability groups (see Table 1 for demographic information).

2.2. Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (Puig-Antich and Chambers, 1978) is a structured

Table 1
Demographics.

| Demographic | High-risk | Low-risk |
|------------------|--------------|--------------|
| Age (mean (SD)) | 13.82 (0.75) | 13.54 (0.88) |
| Race | | |
| African American | 1 | 2 |
| Native American | 1 | 0 |
| White | 8 | 10 |
| Multiple | 1 | 1 |
| Hispanic | | |
| Yes | 2 | 0 |
| No | 9 | 13 |

Note. All participants are female.

interview used to assess diagnostic symptoms of DSM-IV psychiatric disorders, including MDD, in children and adolescents. We used an adapted version of the K-SADS Present and Lifetime Version (K-SADS-PL), combining features of the epidemiological and the present episode versions, to screen for current and past MDD in the adolescent girls (Kaufman et al., 1997). K-SADS interviews were conducted as a prescreening measure over the phone and again in person on the day of the scanning procedure. Girls who met criteria for current or past history of MDD (i.e., 5 symptoms at a severity and duration consistent with DSM-IV criteria for MDD) either over the phone or during the laboratory visit were excluded from the study.

Demographic questionnaire. A demographic questionnaire was used to assess the age, gender, race, psychiatric history, treatment history, and history of psychiatric illness in immediate and extended family.

Structured Clinical Interview for DSM-IV (SCID). The Structured Clinical Interview for DSM-IV Disorders (First et al., 2002) was used to assess current and past history of MDD in the parent of the adolescent participants. Two highly trained assessors conducted all interviews over the phone. Interviews were limited to current and past history of depression sections of the mood module. These sections allowed us to confirm the key inclusion/exclusion criteria in parents of prospective adolescent participants. Parents who reported a current history of depression were excluded from the study (along with their daughters). Daughters of parents who reported a past history of depression on this measure were assigned to the high-risk group. Daughters of parents who reported no history of depression on this measure were assigned to the low-risk group.

Beck Depression Inventory-II (BDI-II). The Beck Depression Inventory-II (Beck et al., 1996) was used to verify that parents were not currently depressed on the day of the scanning procedure. The BDI-II is a widely used self-report questionnaire that assesses depression severity. It consists of 21 items and measures the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression. The BDI-II is valid in both inpatient and outpatient samples and has demonstrated adequate test–retest reliability (Beck et al., 1988).

Patient Health Questionnaire-9 (PHQ-9). The Patient Health Questionnaire (PHQ) is a self-report measure used to assess common mental health disorders in primary care (Spitzer et al., 1999). The PHQ-9 is the depression module of this questionnaire used to assess all 9 of the DSM-IV symptom criteria for depression using a “0” (not at all) to

“3” (nearly every day) scale. It has demonstrated adequate internal and external validity and reliability (Kroenke et al., 2001). This measure was administered to the same parent who completed to SCID interview on the day of scanning. It was used to assess the severity of the parent’s worst lifetime depressive episode. While the BDI-II is commonly administered to assess current depression severity, it is not typically used to assess depression history or severity of past episodes. The PHQ-9 is a brief, psychometrically sound questionnaire that was developed in part for this purpose. The parent of one individual in the non-vulnerable group did not complete the PHQ-9. This individual was not included in the exploratory analysis of the relationship between parental depression severity and functional connectivity (see below).

MRI Scanning Acquisition. All MRI scans were acquired on a whole body 3 T GE scanner with an 8-channel phase array head coil at the Imaging Research Center, University of Texas at Austin. The scanning protocol involved collection of a localizer followed by a high-resolution structural scan, a series of functional scans, a second high-resolution structural scan, and a diffusion tensor scan. The series of functional scans included both resting-state and task-based protocols. The resting state scan always occurred before the performance of any task-based scanning. This manuscript is limited to analysis of high-resolution structural scans and the resting-state scans.

The primary structural scans utilized 3D SPGR volume acquisitions with 1.4 mm thick sagittal slices for a total of 134 slices (Flip=10 degrees, repetition time (TR)=9.7 ms, echo time (TE)=4 ms, inversion time (TI)=20 ms, dwell time (TD)=0 ms, field of view (FOV)=25 cm, Matrix=256 × 256, number of repetitions (NEX)=1). Functional images were acquired using a GRAPPA parallel imaging EPI sequence that reduces typical EPI distortions and susceptibility artifacts. Images were collected utilizing whole head coverage with slice orientation to reduce artifact (approximately 20 degrees off the AC-PC plane and oriented for best whole head coverage, TR=2000 ms, GRAPPA acceleration factor of two, TE=30 ms, 31 axial slices, voxel size=3.125 mm × 3.125 mm × 3 mm with a 0.6 mm interslice gap). The first four EPI volumes were discarded to allow scans to reach equilibrium. Resting state scan instructions were presented utilizing a back projection screen located in the MR bore and viewed through a mirror mounted on the top of the head coil. Head motion was minimized with foam inserts.

Resting-state scan instructions. Prior to the acquisition of resting-state scans participants were instructed to remain awake and alert and keep their gaze on a fixation cross (+) presented approximately at the center of their field of view for the 6-min duration of the scan.

Analysis plan. Data were processed using FSL’s FMRI Expert Analysis Tool (FEAT version 5.98) (Smith et al., 2004). Functional, blood oxygen level dependent (BOLD), volumetric time series were corrected for motion, spatially smoothed using a 6 mm Gaussian filter, high pass filtered (100 s). Seed-based functional connectivity analyses were then performed on the residual 4D volumes after motion parameters and the global mean were modeled as nuisance

variables. The global mean signal was removed (using FSL's intensity normalization tool) so our results were not driven by spontaneous fluctuations that are common across the whole brain (Fox et al., 2009).

We took a conservative, unbiased approach to seed selection: The rIFG seed used in this study consisted of an 8 mm sphere centered on the peak location from a rIFG ROI identified in a previously reported whole brain analysis of attentional biases in dysphoric adults (Montreal Neurological Institute (MNI) coordinates [$x = 52, y = 12, z = 8$], see Fig. 1 for seed location; Beever et al., 2010). The seed was translated from MNI standard space to individual native space and the BOLD time series from this seed was extracted for each individual. The native space seed time-series was then correlated against all other voxels within the brain (using FEAT) to generate whole brain Pearson correlation coefficient (r) maps. These maps were then normalized using Fisher's r -to- z transform ($z = 0.5 \ln[(1+r)/(1-r)]$) to correct for non-normality in the distribution of r -values within individual omnibus functional connectivity maps. Results were then translated to standard space (MNI) in preparation for group level hypothesis testing.

Group level contrasts involved the following steps using FSL's FEAT. First, a full group connectivity map was generated reflecting whole brain correlations with the seed region that survived a cluster corrected $p < 0.05$ threshold. Next, a priori contrasts were performed to explore group differences based on parental history of depression (low-risk vs. high-risk). These two-sample t -tests were only carried out in voxels that showed significant connectivity across the entire group and cluster corrected at a $p < 0.05$ threshold. Beyond these restricted whole brain contrasts, we examined differences in connectivity between the seed and a priori target locations in the rMFG and rSMG (MNI coordinate locations: rMFG [$x = 44, y = 2, z = 34$]; rSMG [$x = 50, y = -34, z = 42$]). Again, these targets consisted of 8 mm spheres centered on peak locations from our previous study (see Fig. 2 for ROI locations) (Beever et al., 2010). Fisher z -transformed r -values were extracted from these locations for each individual from the full group connectivity map. Next, two-sample t -tests were performed on these values based on group assignment (low-risk vs. high-risk). Results were corrected for multiple comparisons using a Bonferroni correction. Finally, we performed an exploratory post hoc analysis examining the relationship between parents' worst episode of depression and connectivity between the rIFG seed and rMFG/rSMG targets respectively. Fisher z -transformed r -values extracted from these target locations were regressed on parents' PHQ-9 scores. This analysis was conducted for all participants, irrespective of assignment to vulnerability groups. Results were corrected for multiple comparisons using a Bonferroni correction. It is important to emphasize that these target ROIs were not generated from the whole brain analysis, but come from a previous study of attentional control in dysphoric adults (Beever et al., 2010) and were selected a priori. This analysis is included to test whether whole brain findings in the adolescent sample map onto key nodes of a network implicated in the adult literature and more specifically test the relationship between parental severity of depression and connectivity within this network.

Procedure. Participants and their parent completed the phone-screening interview with a trained researcher to assess for (1) current or past history of depression in the adolescent, (2) current or past history of depression in the parent, (3) MRI contraindications in the adolescent. Participants and parents who met study criteria were invited to the Imaging Research Center at The University of Texas at Austin. After reviewing the consent form in detail, the participant's parent was asked to provide written informed consent and the participant was asked to provide written assent for participation. Next, participants completed the imaging protocol, including structural and functional scans. Then, participants completed a diagnostic interview and several questionnaires. Participants also provided a sample of saliva for genetic analysis; this will not be included in this manuscript. After completing all study protocols, participants were thanked for their time and compensated \$100 per family.

3. Results

3.1. Seed connectivity whole-brain, by group

Whole-brain omnibus functional connectivity maps are plotted for each group (low- and high-risk) in Fig. 1 (panels (a) and (b), respectively). The seed location is specified in the center of each panel and connectivity plots for left and right-hemispheres are arranged on each side. These maps demonstrate that, as expected, regions of the CCN – including bilateral dorsal lateral prefrontal cortex, anterior cingulate, and supramarginal gyrus – reveal significant connectivity with the rIFG seed location in both high-risk and low-risk groups. Visual inspection of these maps demonstrates the degree of similarity among regions showing significant functional connectivity across groups. Next, we formally tested between group differences in functional connectivity.

Group comparisons. Group contrast maps for the low-risk > high-risk comparison are plotted in Fig. 2. This plot indicates higher levels of connectivity between the rIFG seed and regions of right dorsal lateral prefrontal cortex and left and right mesial prefrontal cortex in the low-risk group relative to the high-risk group. Peak location coordinates, cluster sizes, and p -values are listed in Table 2. There were no significant differences for the high-risk > low-risk comparison. Because recent work has shown that head movement can systematically influence estimates of resting state functional connectivity, particularly in between group comparisons (Power et al., 2012), we examined the mean framewise displacement (FD) values for differences between groups. FD provides an index of instantaneous head movement for every volume (TR) of each participant's resting state time-series. There was no significant difference between the high-risk and low-risk groups on this measure, $t(22) = -0.74, p = 0.46$. These findings support the hypothesis that adolescent women with a parental history of depression demonstrated lower levels of functional connectivity between nodes of the CCN that may underlie attentional control for emotional information.

ROI analysis. Using a priori, unbiased ROIs in rMFG and rSMG we tested for differences between high-risk

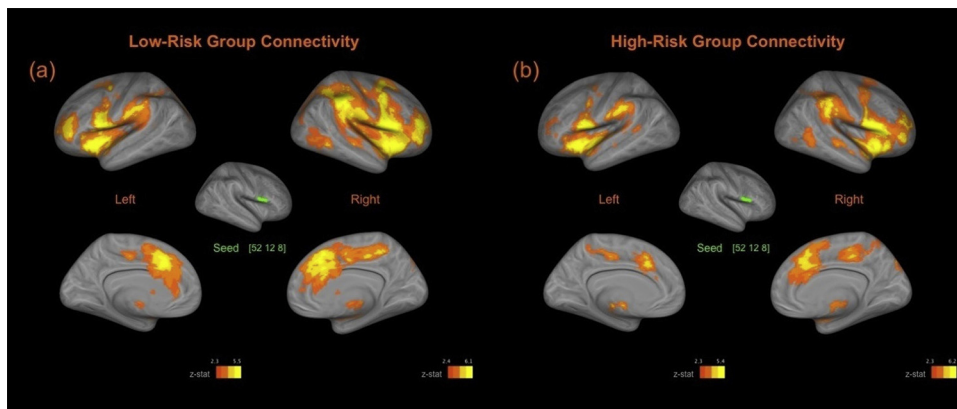


Fig. 1. Whole brain functional connectivity with right inferior frontal gyrus seed by group. Panel (a) reflects functional connectivity in the low-risk group. Panel (b) reflects functional connectivity in the high-risk group. Orange/Yellow overlays represent regions showing significant correlations with seed region (in green, at center of each panel) at cluster corrected $p < 0.05$ threshold projected onto inflated cortical surface renderings. (For interpretation of color in the artwork, the reader is referred to the web version of the article.)

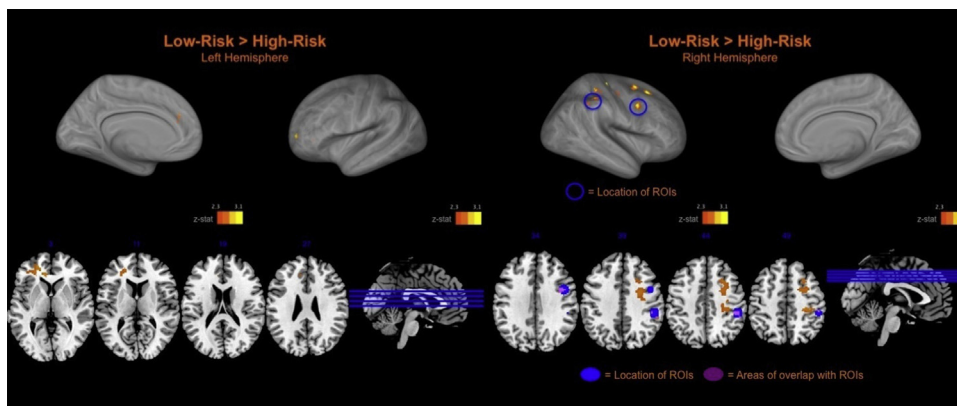


Fig. 2. Whole brain group differences in connectivity with right inferior frontal gyrus seed (Low-Risk > High-Risk). Orange/Yellow overlays represent regions showing significant differences in connectivity with seed region by group (Low-Risk > High-Risk) at cluster corrected $p < 0.05$ threshold. Whole brain differences are shown on inflated cortical surface renderings (above) as well as axial slice renderings (below) for each hemisphere. Slice locations (z MNI coordinate) are noted in blue above each slice. Locations for Region of Interest (ROI) analysis are shown in blue in the Right Hemisphere panel. Areas of overlap between the whole brain group contrast and ROI locations are shown in purple. (For interpretation of color in the artwork, the reader is referred to the web version of the article.)

and low-risk groups. These ROIs overlap with locations from whole brain analysis and are indicated in Fig. 2 (blue circles). Results of the ROI analysis are plotted in Fig. 3. In both ROIs, connectivity was significantly greater for the low-risk than the high-risk group: rIFG-rMFG connectivity X group, $t(22) = 2.64$, $p = 0.03$, $\text{cohen's } d = 1.13$ (Fig. 3a); rIFG-rSMG connectivity X group, $t(22) = 2.69$, $p = 0.028$, $\text{cohen's } d = 1.15$ (Fig. 3b).

In order to further rule out that these results reflect differences in motion between groups we performed a “motion scrubbing” procedure, recommended by Power

et al. (2012), to mitigate the influence of head motion on functional connectivity estimates. The first step of this procedure involves thresholding the time series to determine frames containing high motion for removal. A conservative FD threshold of 0.2 mm was adopted based on visual inspection of the FD plots across participants. Within each participant's time series, volumes that exceeded this threshold were flagged and removed. To accommodate temporal smoothing of BOLD data processing, the volume before and two volumes after each flagged volume were also removed. Participants with fewer than 100 volumes

Table 2

Peak coordinate locations for whole brain group differences in connectivity with right inferior frontal gyrus seed (Non-Vulnerable > Vulnerable). Region, number of voxels, Z-MAX, and MNI coordinates.

| Location | Number of voxels | Z-MAX | Z-MAX MNI coordinates | | |
|--|------------------|-------|-----------------------|-----|----|
| | | | X | Y | Z |
| Right – middle frontal gyrus/supramarginal gyrus | 618 | 3.39 | 26 | –28 | 48 |
| Left – frontal pole | 302 | 3.54 | –22 | 50 | 4 |
| Left – anterior cingulate | 16 | 2.77 | –10 | 36 | 26 |

Region of Interest (ROI) comparisons

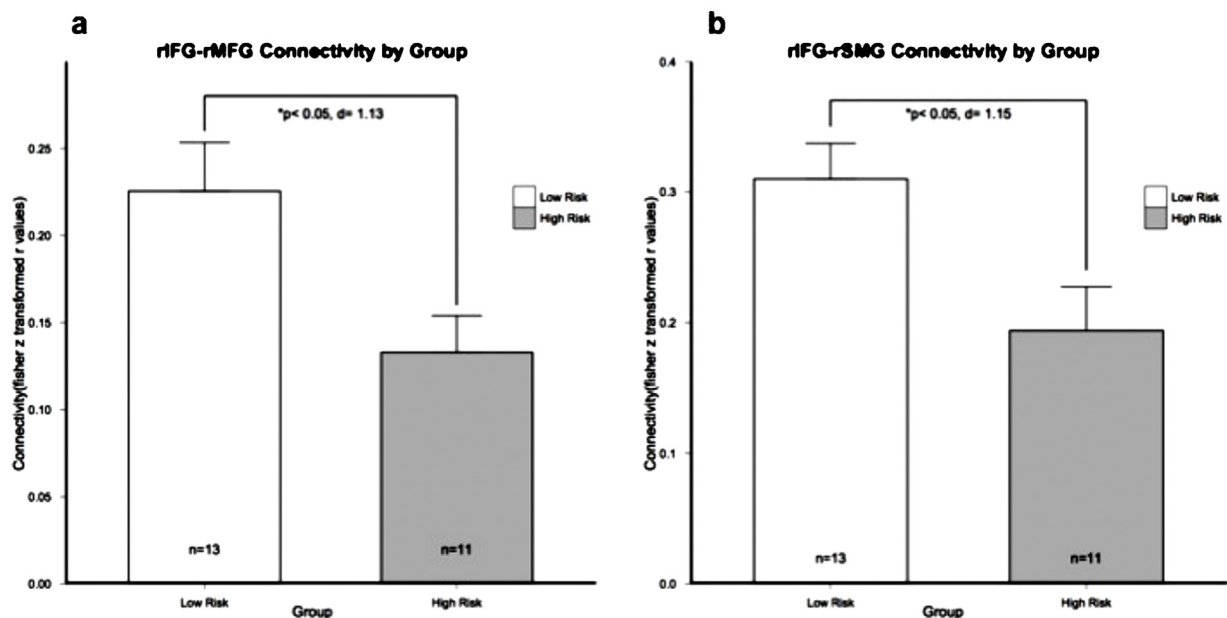


Fig. 3. Region of interest (ROI) analysis (prior to motion scrubbing ($N=24$)). Panel (a) represents group differences in connectivity between the right inferior frontal gyrus (rIFG) seed and the right middle frontal gyrus (rMFG) ROI. Panel (b) represents group differences in connectivity between the rIFG seed and the right supramarginal gyrus (rSMG) ROI.

remaining following this “motion scrubbing” procedure were excluded from this follow up analysis. This led to the exclusion of 5 participants (2 high-risk, 3 low-risk).

Results of the ROI analysis performed after motion scrubbing ($N=19$) are plotted in Fig. 4. Again, in both ROIs, connectivity was significantly greater for the low-risk than the high-risk group: rIFG-rMFG connectivity X group, $t(17)=2.25$, $p=0.04$, *cohen's d*=1.09 (Fig. 4a); rIFG-rSMG connectivity X group, $t(17)=2.36$, $p=0.03$, *cohen's d*=1.15 (Fig. 4b). These results suggest that despite the reduced power associated with significant data loss following motion scrubbing, the high-risk group continues to demonstrate a similar magnitude of greater connectivity between the rIFG seed and the a priori ROIs in rMFG and rSMG.

Parent's worst episode depression severity. Finally, we explored whether individual differences in the severity of the parents' worst lifetime episode of depression (across the whole group) predicted functional connectivity between our unbiased ROIs and the rIFG seed. While parents in the high risk group rated their worst episode of depression on this measure, those in the low risk group rated their worst experience of depression symptoms regardless of whether this met clinical criteria for an episode. The correlation between parental severity and risk group assignment (high vs. low) is $r=0.71$, $p=0.002$, suggesting that while group assignment is highly indicative of past depression severity, it does not account for all the variance in this measure. We included this analysis to explore whether the severity of past depression symptoms, irrespective of clinical criteria for an episode, is associated with cognitive control network connectivity. This approach

is consistent with dimensional models of psychopathology including the Research Domain Criteria (RDoC) approach advanced by the National Institute of Mental Health (e.g., Insel et al., 2010). Results from the analysis prior to motion scrubbing ($N=24$) are plotted in Fig. 5a and indicate that more severe depression in parents correspond with lower levels of functional connectivity between nodes of the CCN, $t(21)=-2.29$, $p=0.03$, *effect size* $r=-0.45$. These findings suggest that individual differences in the severity of parents' depression history are associated with the development of neural networks underlying cognitive control for emotional information in their adolescent daughters. Results from the motions scrubbed data ($N=19$) further support this conclusion, $t(17)=-2.16$, $p=0.045$, *effect size* $r=-0.46$ (see Fig. 5b).

4. Discussion

This study aimed to identify differences in the neural systems underlying cognitive control for emotional information among adolescent women who are at risk for depression based on a parental history of MDD. Using functional connectivity analysis within a circumscribed network of brain regions underlying cognitive control, we found that girls with a parental history of depression showed decreased connectivity between key brain regions implicated in attentional control for emotional information. Specifically, girls with a parental history of depression showed decreased connectivity between right inferior frontal gyrus (rIFG) and locations in right middle frontal gyrus (rMFG) and right supramarginal gyrus (rSMG). They also showed decreased connectivity between

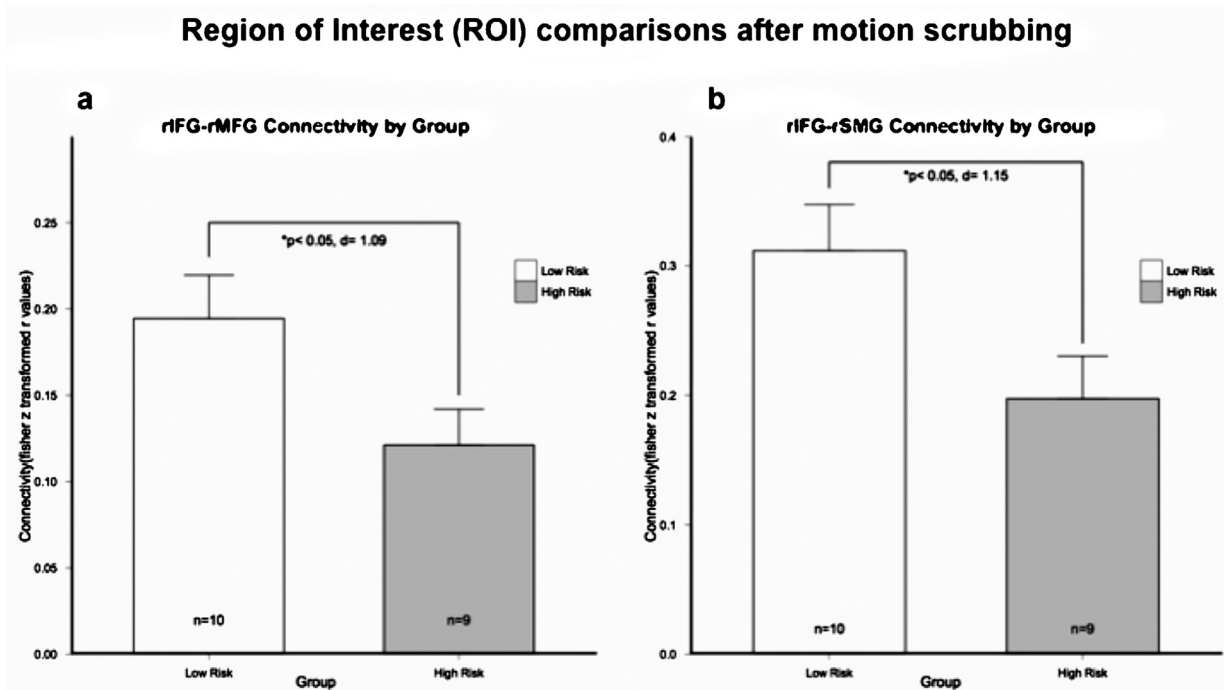


Fig. 4. Region of interest (ROI) analysis (after motion scrubbing ($N = 19$)). Panel (a) represents group differences in connectivity between the right inferior frontal gyrus (rIFG) seed and the right middle frontal gyrus (rMFG) ROI. Panel (b) represents group differences in connectivity between the rIFG seed and the right supramarginal gyrus (rSMG) ROI.

rIFG-rMFG Connectivity in Child (as a function of parent's worst episode depression)

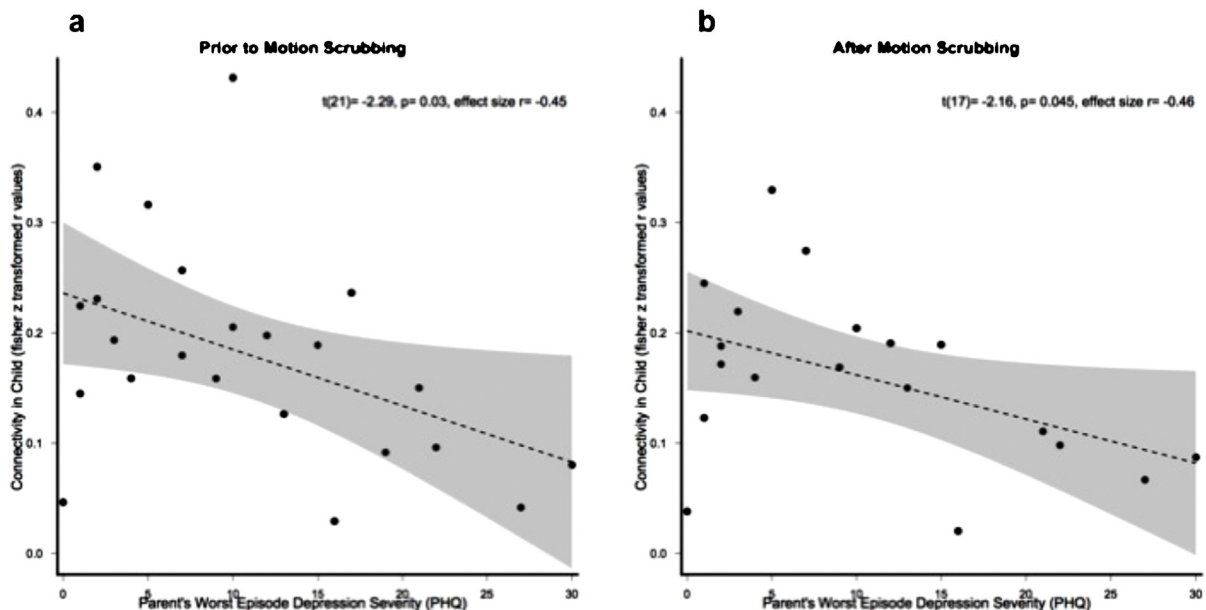


Fig. 5. Relationship between severity of parents' worst episode of depression and connectivity between right inferior frontal gyrus seed and the right middle frontal gyrus target. Panel (a) represents this relationship prior to the application of the motion scrubbing procedure ($N = 24$). Panel (b) represents this relationship after the application of the motion scrubbing procedure ($N = 19$).

rIFG and regions of left frontal pole (IFP) and left anterior cingulate cortex (IACC). Exploratory analysis demonstrated that the severity of the parents' worst episode of depression was negatively associated with connectivity between right IFG and MFG locations. These findings support the hypothesis that daughters of parents with a depression history reveal an underdeveloped functional connectivity within neural systems underlying attentional control for emotional information. It is important to note that these findings cannot be attributed to between group differences in motion as they remain after a rigorous approach to removing the influence of head motion on resting state functional connectivity estimates.

To our knowledge, this study represents the first exploration of CCN connectivity in this high-risk population. Our findings are in line with a limited number of resting state functional connectivity analyses among individuals with adolescent depression. These studies did not examine CCN connectivity directly, however, they report a similar pattern of decreased connectivity in resting state networks that are similarly associated with adult depression (Bluhm et al., 2009; Cullen et al., 2009). Moreover, they are in line with recent resting state functional connectivity analyses of the CCN in depressed adults (Veer et al., 2010; Alexopoulos et al., 2012), suggesting a pattern of decreased functional connectivity within this network. Our data extend this research in two important ways. First, they suggest that adolescent women who are high risk for depression, but have never been depressed, show a similar pattern of decreased connectivity within the CCN. Second, they highlight the possibility that the functional development of the CCN is a critical mechanism associated with depression vulnerability. Indeed, findings from the current study provide the first demonstration that CCN connectivity alterations predate the onset of depression.

These findings fit broadly into an integrated cognitive-neural model of depression. This model suggests that diminished recruitment of CCN regions influence depression vulnerability and maintenance via effects on cognitive control for emotional information (De Raedt and Koster, 2010; Disner et al., 2011). In other words, neural deficits are thought to underlie difficulties with basic cognitive control mechanisms (e.g., attentional control, inhibition, reappraisal) that support emotion regulation. These deficits may handicap the performance of this network and, therefore, negatively impact vulnerable individuals' ability to regulate negative information during a stage of development when this skill becomes increasingly important (Nolen-Hoeksema, 1994; Cyranowski et al., 2000; Hankin and Abramson, 2001). Indeed, cognitive models of depression suggest that over time such difficulties may confer vulnerability for the onset of depression, particularly in the context of stressful life events (Beevers et al., 2011).

These findings are also in line with evidence of behavioral deficits in cognitive control over emotional information in this population. Recent reaction time studies suggest that adolescent women with a parental history of depression demonstrate deficits in attentional control for mood congruent stimuli (Joormann et al., 2007; Gibb et al., 2009). Our findings suggest that these behavioral deficits may correspond to abnormalities in CCN functional

connectivity. Of course, the current study does not directly assess the relationship between differences in functional connectivity and behavioral deficits in attentional control in this population. This question remains an important area for future research.

Another exciting avenue for future research involves the potential to prevent depression in this high-risk population by enhancing CCN functional connectivity. Recent work using real-time neural feedback suggests that training people to modulate activity in a specific brain region can influence connectivity with regions in putative resting state networks (Hamilton et al., 2011). Our findings highlight a key region that may be targeted in similar paradigms (rIFG) as a means of modulating CCN connectivity. Future work is required to investigate the whether this intervention helps bolster cognitive control for emotional information among young women with a parental history of MDD and whether this, in turn, helps reduce depression vulnerability in this population.

Of course, our findings should be interpreted in the context of several important limitations. First, our sample size is relatively small. Efforts to replicate should consider enrolling a larger sample, although we note that this is the first study to examine CCN connectivity in adolescents at high-risk for depression. Given this relatively small sample it is important to apply appropriate caution when considering the implications of these findings until these data are replicated with a larger sample. Second, the cross-sectional design did not involve follow-up with research participants. Therefore, we were not able to determine if differences in CCN connectivity predicted depression onset. Including longitudinal follow up is a critical feature of future research to directly assess the extent to which differences in connectivity predict depression onset, particularly in the context of life stress. Third, we only measured one parent's depression history. It is possible that some individuals in the non-vulnerable group, in fact, should have been assigned to the vulnerable group if their other parent had a history of depression. We used a self-report check to screen for this and successfully removed two participants, however, future work should consider measuring full inclusion/exclusion criteria in both parents.

Despite these limitations, we believe this study represents an important contribution to our understanding of the neural mechanisms underlying depression vulnerability in this high-risk population. Women with a parental history of depression are uniquely vulnerable for the onset of MDD, an onset that carries significant short and long-term consequences. This research is an important first step toward elucidating the neural mechanisms underlying this vulnerability; an effort that, ultimately, may facilitate interventions aimed at preventing the consequences of adolescent depression in this high-risk population.

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